Salicylazosulfapyridine

CAS #599-79-1
CD (Sprague-Dawley) rats, at 0.0, 100, 200, and 400 mg/kg by gavage
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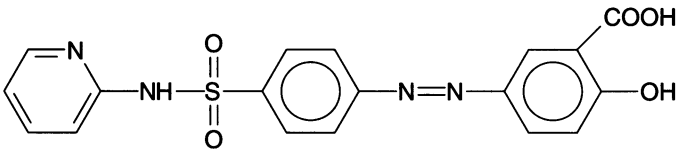

Salicylazosulfapyridine (SASP) is a sulfonamide used to treat inflammatory bowel disease and ulcerative colitis. Although several case reports existed concerning the ability of SASP to adversely affect male reproduction, there were few data on fertility, and no publicly available data on potential effects of SASP on female fertility. It was tested for its effects on reproduction and fertility in Sprague-Dawley rats using the RACB protocol. Data on food and water consumptions, body weights, and clinical signs from the dose-range-finding study (Task 1) were used to set exposure concentrations for the continuous cohabitation phase (Task 2) at 100, 200, and 400 mg/kg, administered by gavage.

Three controls, one low dose, and three high dose rats died on study. Most of these deaths were related to gavage injury; one death was from uterine hemorrhage. Water consumption was increased 10 to 30% in treated rats, proportional to dose. Dam weights taken after delivery of each litter showed the high dose females weighed slightly less than controls (significantly so for the second and fourth litters); male weights were reduced only after week 10 in the high dose group, by 7 to 12%.

While the mean number of litters per pair was not changed by SASP, the mean number of pups per litter was reduced by 14, 33, and 31% (low to high dose groups, respectively). The weight of these pups, adjusted for litter size, was reduced only at the high dose by 8%. Cumulative days to deliver each litter was unchanged by SASP exposure.

The last litter was reared by the dams until weaning, whereupon the F_1 rats from all dose levels were gavaged at the same dose received by their parents. Pup survival and growth during nursing was not adversely affected by SASP treatment; pups in the middle dose group weighed more than controls on postnatal day 14 and 21.

When the last litter was weaned, a modified crossover was performed. This incorporated a dominant lethal evaluation, wherein the dams were killed gestational day 19 and uterine contents examined, using the control and high dose groups. For the group mating treated males to control females, only two thirds of the sperm-positive females delivered live young. This group also had a 74% reduction in the number of live implants per litter, and no increase in deads. The only increase in "pre-implantation loss" occurred in treated males. Collectively, the male data are consistent with a failure of fertilization. Although the treated females had 20% fewer corpora lutea, the reductions in number of live implants were not statistically significant. The number of resorptions per litter was not increased for the treated females.

All F_0 groups were killed and necropsied after the crossover. Male body weight was reduced by 9 and 16% in the middle and high dose groups; absolute testis weight was increased by 9% at 100 mg SASP/kg. Body weight-adjusted epididymis weight was increased by 8%, while adjusted kidney weight was increased in all dosed groups, by 8 to 17%. Epididymal sperm density was reduced only at the middle dose level (by 23%), while the percent abnormal forms rose from a control value of 0.89% to approximately 4% in all treated groups.

For females, only the controls and high dose F_0 rats were necropsied. Body weights were reduced at 400 mg/kg by 12%, while body weight-adjusted liver and kidney weights were increased by 9%.

No significant microscopic lesions were seen in the gonads and accessory sex organs of rats in any dose group. Because previous studies in rodents suggested an epididymal site of action for SASP, serum levels of acidic epididymal glycoprotein (AEG) measured by radioimmunoassay were determined; these were unchanged by SASP exposure. Also, because SASP is known to be goiterogenic, blood thyroid-stimulating hormone (TSH) levels were measured in the F_0 rats. TSH levels were increased only at the high dose level, to 167% (males) and 232% (females) of control.

The second generation was mated within dose groups at approximately postnatal day 74. There was no significant change (or trend) in the mating, pregnancy, or fertility index nor in the number of live pups per litter. Adjusted pup weight was reduced in the middle and high dose groups by 10 and 12%, respectively. Mean dam weight was reduced only at the high dose level by 11%.

After the F_2 rats were delivered and evaluated, F_1 rats from all dose levels were killed and necropsied. Male body weight was reduced only at the high dose, by 9%, while adjusted liver weight was reduced by 6 and 4% (middle and high dose, respectively), and adjusted kidney weight was increased at the middle and high doses by 9 and 11%. Absolute testis weight was increased in the low through high dose groups, by 13, 17, and 28%, respectively. There was a dose-related increase in thyroid weight which reached significance at the high dose (18%). Epididymal sperm density and motility were generally unchanged, while the percent abnormal forms rose slightly from 0.84% (controls) to approximately 3% in all treated groups.

Female body weight was reduced by 9% at the top dose. Adjusted kidney weight was increased at the top dose by 10%, while thyroid weight again showed a

dose-related increase that was significant at the high dose (37%). Antemortem vaginal cyclicity was unchanged at any level of SASP consumption.

Thyroid follicular hyperplasia was noted microscopically for both sexes; other microscopic findings were largely incidental. While acidic epididymal glycoprotein levels were unchanged by SASP exposure, serum TSH levels were increased to 168 and 307% of control values for high dose males and females, respectively.

In the presence of modest changes in body weight, SASP reduced male fertility at doses that left most sperm indices functionally unchanged. One circulating measure of epididymal function, serum AEG levels, were consistently unchanged by SASP. There were clear indications of reduced thyroid output, registered as increased serum TSH levels, increased F_1 thyroid weights, microscopic findings of such stimulation, and increased F_1 testis weights. Treated females were also found, in the dominant lethal study, to release fewer ova. Overall, there were no indications of dominant lethality, but evidence of decreased gamete or gametogenic function, evidenced by fewer implants from treated males, and fewer corpora lutea in treated females.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB92203710**
Chemical: **Salicylazosulfapyridine**
CAS#: **599-79-1**
Mode of exposure: **Gavage**
Species/strain: **SD rats**

F_0 generation — Dose concentration →	100 mg/kg	200 mg/kg	400 mg/kg
General toxicity	Male, female	Male, female	Male, female
Body weight	—, —	↓, —	↓, ↓
Kidney weight[a]	↑, •	↑, •	↑, ↑
Liver weight[a]	—, •	—, •	—, ↑
Mortality	—, —	—, —	—, —
Feed consumption	•	•	•
Water consumption	↑, —	↑, ↑	↑, ↑
Clinical signs	—, —	—, —	—, —
Reproductive toxicity			
x̄ litters/pair	—	—	—
# live pups/litter; pup wt./litter	↓, —	↓, —	↓, ↓
Cumulative days to litter	—	—	—
Absolute testis, epididymis weight[a]	↑, —	—, —	—, ↑
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, —	—, —	↑, ↑
Epidid. sperm parameters (#, motility, morphology)	—, —, ↑	↓, —, ↑	—, —, ↑
Estrous cycle length	•	•	•

Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	—	400 mg/kg

F_1 generation — Dose concentration →	100 mg/kg	200 mg/kg	400 mg/kg
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	—, —	↑, ↑	—, —
Mortality	—, —	—, —	—, —
Adult body weight	—, —	—, —	↓, ↓
Kidney weight[a]	—, —	↑, —	↑, ↑
Liver weight[a]	—, —	↓, —	↓, —
Feed consumption	•	•	•
Water consumption	—, —	—, —	—, —
Clinical signs	—, —	—, —	—, —
Reproductive toxicity			
Fertility index	—	—	—
# live pups/litter; pup wt./litter	—, —	—, —	—, —
Absolute testis, epididymis weight[a]	↑, —	↑, —	↑, ↑
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, —	—, —	—, ↑
Epidid. sperm parameters (#, motility, morphology)	—, ↑, ↑	—, —, ↑	—, —, ↑
Estrous cycle length	—	—	—

Summary information	
Affected sex?	Male
Study confounders:	None
NOAEL reproductive toxicity:	<100 mg/kg
NOAEL general toxicity:	<100 mg/kg
F_1 more sensitive than F_0?	No
Postnatal toxicity:	No

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); —, —, no change in males or females. [a]Adjusted for body weight.